



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 5/03, C07D 209/48, 401/12, 403/12, 413/12, A61K 38/06, 31/40, 31/435, 31/495, 31/535		A1	(11) International Publication Number: WO 96/35712 (43) International Publication Date: 14 November 1996 (14.11.96)
(21) International Application Number: PCT/GB96/01135 (22) International Filing Date: 10 May 1996 (10.05.96) (30) Priority Data: 9509404.1 10 May 1995 (10.05.95) GB 9525646.7 15 December 1995 (15.12.95) GB 9607154.3 4 April 1996 (04.04.96) GB (71) Applicant: CHIROSCIENCE LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (72) Inventors: BAXTER, Andrew, Douglas; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). MONTANA, John; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). OWEN, David, Alan; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).		(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: PEPTIDYL COMPOUNDS WHICH INHIBIT METALLOPROTEINASE AND TNF LIBERATION AND THEIR THERAPEUTIC USE (57) Abstract Dipeptidyl derivatives having a SH or acylS group and which are amides, thioamides or S(O) ₀₋₂ -amides, have therapeutic utility via MMP or TNF inhibition.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

PEPTIDYL COMPOUNDS WHICH INHIBIT METALLOPROTEINASE AND TNF LIBERATION AND THEIR THERAPEUTIC USE**Field of the Invention**

This invention relates to a novel class of peptidyl derivatives, to processes for their preparation, and to their use in medicine.

5 Background to the Invention

In normal tissues, cellular connective tissue synthesis is offset by extracellular matrix degradation, the two opposing effects existing in dynamic equilibrium. Degradation of the matrix is brought about by the action of proteinases released from resident connective tissue cells and invading inflammatory cells, and is due, in part,
10 to the activity of at least four groups of metalloproteinases. These are the collagenases (interstitial collagenase, MMP-1; PMN collagenase, MMP-8, collagenase-3, MMP-13), the gelatinases (gelatinase A, MMP-2, 72kDa-gelatinase, Type IV collagenase; gelatinase B, MMP-9, 92kDa-gelatinase, Type IV collagenase) the stromelysins (proteoglycanase, MMP-3, stromelysin-1, transin; stromelysin-2,
15 MMP-10; stromelysin 3, MMP-11) and the membrane type matrix metalloproteinases (MT-1, MMP-14; MT-2, MMP-15; MT-3, MMP-16 and MT-4, MMP-17). Normally these catabolic enzymes are tightly regulated at the level of their synthesis and secretion and also at the level of their extracellular activity, the latter through the action of specific inhibitors, such as TIMP (tissue inhibitors of
20 metalloproteinase), which form inactive complexes with metalloproteinases, and more general proteinase inhibitors such as α_2 -macroglobulins.

The accelerated, uncontrolled breakdown of connective tissues by metalloproteinase catalysed resorption of the extracellular matrix is a feature of many pathological conditions such as rheumatoid arthritis, osteoarthritis, septic arthritis,
25 corneal, epidermal or gastric ulceration; tumour metastasis or invasion; periodontal disease, proteinuria, coronary thrombosis associated with atherosclerotic plaque rupture and bone disease. Inhibitors may also be useful in preventing the pathological squaelae following a traumatic injury that could lead to a permanent disability. These compounds may also have utility as a means for birth control by
30 preventing ovulation or implantation. It can be expected that the pathogenesis of such diseases is likely to be modified in a beneficial manner by the administration of metalloproteinase inhibitors and numerous compounds have been suggested for

this purpose [for a general review see R C Wahl, *et al* Ann. Rep. Med. Chem. 25: 175-184, Academic Press Inc., San Diego (1990)].

A number of small peptide like compounds which inhibit metalloproteinases have been described. Perhaps the most notable of these are those relating to angiotensin converting enzyme (ACE) where such agents act to block the conversion of the decapeptide angiotensin I to angiotensin II, a potent pressor substance. Compounds of this type are described in EP-A-0012401. Also, related mercaptoamide peptidyl derivatives have shown ACE inhibitor activity *in vitro* and *in vivo* (H N Weller *et al* (1984), Biochem Biophys. Res. Comm., 125 (1):82-89).

TNF is a cytokine which is produced initially as a cell-associated 28kD precursor. It is released as an active, 17kD form (D-M Jue *et al*, (1990) Biochemistry, 29:8371-8377), which can mediate a large number of deleterious effects *in vivo*. When administered to animals or humans it causes inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase responses, similar to those seen during acute infections and shock states. Chronic administration can also cause cachexia and anorexia. Accumulation of excessive TNF can be lethal.

There is considerable evidence from animal model studies that blocking the effects of TNF with specific antibodies can be beneficial in acute infections, shock states, graft versus host reactions and autoimmune disease. TNF is also an autocrine growth factor for some myelomas and lymphomas and can act to inhibit normal haematopoiesis in patients with these tumours.

Preventing the production or action of TNF is, therefore, predicted to be a potent therapeutic strategy for many inflammatory, infectious, immunological or malignant diseases. These include, but are not restricted to, septic shock, haemodynamic shock and sepsis syndrome (Mathison *et al* (1988) J. Clin. Invest. 81:1925-1937; Miethke *et al* (1992), J. Exp. Med. 175:91-98), post ischaemic reperfusion injury, malaria (Grau *et al* (1989), Immunol. Rev. 112:49-70); mycobacterial infection (Barnes *et al* (1992) Infect. Imm. 60:1441-6), meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, rheumatoid arthritis, multiple sclerosis, radiation damage,

toxicity following administration of immunosuppressive monoclonal antibodies such as OKT3 or CAMPATH-1 and hyperoxic alveolar injury.

Current clinical anti-TNF strategies involve the use of corticosteroids such as dexamethasone, and the use of cyclosporin-A or FK506, which are non-specific inhibitors of cytokine gene transcription. Phosphodiesterase inhibitors such as pentoxifylline have been shown to be more specific inhibitors of TNF gene transcription (Endres S. (1991) *Immunol.* 72:56-60, Schandene *et al* (1992), *Immunol.* 76:30-34, Alegre ML, *et al* (1991); Transplantation 52:674-679, Bianco *et al* (1991) *Blood* 78:1205-1221). Thalidomide has also been shown to inhibit TNF production by leucocytes (Sampajo *et al* (1991), *J. Exp. Med.* 173:699-703). In experimental settings, anti-TNF monoclonal antibodies, soluble TNF receptors and soluble TNF receptor/immunoadhesins have been shown to specifically inhibit the effects of TNF action (Bagby *et al* (1991) *J. Infect. Dis.* 163:83-88, Charpentier *et al.* (1991) *Presse-med.* 20:2009-2011, Silva *et al* (1990) *J. Infect. Dis.* 162:421-427; Franks *et al* (1991) *Infect. Immun.* 59:2609-2614, Tracey *et al* (1987) *Nature* 330:662-664; Fischer *et al* (1992) *PNAS USA* in press, Lesslauer *et al* (1991) *Eur. J. Immunol.* 21:2883-2886, Ashkenazi *et al* (1991) *PNAS USA* 88:10535-10539).

It has recently been shown that the effects of TNF are mediated by two peptides, TNFa and TNFb. Although these peptides have only 30% homology with each other, they activate the same receptors and are encoded by immediately adjacent genes. As used herein, the term tumour necrosis factor or TNF therefore means tumour necrosis factor a and peptides having a high degrees of sequence homology with, or substantially similar physiological effects to, TNFa, for example TNFb.

One of the objectives of the present invention is to provide compounds which substantially inhibit the release of TNF from cells, and therefore may be used in the treatment of conditions mediated by TNF. Such uses include, but are not limited to, the treatment of inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, graft versus host reactions and autoimmune disease.

Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF both *in*

vitro and *in vivo* (AJH Gearing *et al* (1994), Nature, 370:555-557; GM McGeehan *et al* (1994), Nature, 370:558-561; MJ Crimmin *et al*, WO 93/20047). All of these reported inhibitors contain a hydroxamic acid zinc binding group.

5 It is, therefore, a further objective of this invention to provide compounds which, in addition to inhibiting TNF release, also inhibit the action of MMPs, and hence may be used in the treatment of patients who suffer from conditions mediated by TNF and/or MMPs.

10 As appreciated by those of skill in the art the significant proportion of homology between human fibroblast collagenase, stromelysin and gelatinase leads to the possibility that a compound that inhibits one enzyme may to some degree inhibit all of them.

Compounds that inhibit collagenase, which possess structural portions akin to those of the instant invention include those encompassed by U.S. 4,511,504 issued Apr. 16, 1985; U.S. 4,568,666, issued Feb 4, 1986.

15 Compounds of related structure that are claimed to inhibit stromelysin (proteoglycanase) are encompassed by U.S. 4,771,037, issued Sept. 13, 1988.

The applicants believe that stromelysin and collagenase inhibitors have utility in preventing articular cartilage damage associated with septic arthritis. Bacterial infections of the joints can elicit an inflammatory response that may then be perpetuated beyond what is needed for removal of the infective agent resulting in permanent damage to structural components. Bacterial agents have been used in animal models to elicit an arthritic response with the appearance of proteolytic activities. See J. P. Case *et al* (1989), J. Clin. Invest., 84:1731-40; R. J. Williams *et al* (1990), Arth. Rheum., 33: 533-41.

25 The applicants also believe that inhibitors of stromelysin, collagenase and gelatinase will be useful to control tumour metastasis, optionally in combination with current chemotherapy and/or radiation. See L. M. Matrisian *et al* (1986), Proc. Natl. Acad. Sci., USA, 83:9413-7; S. M. Wilhelm *et al* (1987), Ibid. 84:6725-29; Z. Werb *et al* (1989), J. Cell Biol., 109:872-889; L. A. Liotta *et al* (1983), Lab. Invest., 49:636-649; R. Reich *et al* in Metastasis; Ciba Foundation Symposium, Wiley, Chichester, 1988, pp. 193-210.

Secreted proteinases such as stromelysin, collagenase and gelatinase play an important role in processes involved in the movement of cells during metastatic tumour invasion. Indeed, there is also evidence that the matrix metalloproteinases are overexpressed in certain metastatic tumour cell lines. In this context, the enzyme functions to penetrate underlying basement membranes and allow the tumour cell to escape from the site of primary tumour formation and enter the circulation. After adhering to blood vessel walls, the tumour cells use these same metalloproteinases to pierce underlying basement membranes and penetrate other tissues, thereby leading to tumour metastasis. Inhibition of this process would prevent metastasis and improve the efficacy of current treatments with chemotherapeutics and/or radiation.

These inhibitors should also be useful for controlling periodontal diseases, such as gingivitis. Both collagenase and stromelysin activities have been isolated from fibroblasts derived from inflamed gingiva (V. J. Uitto *et al* (1981), *J. Periodontal Res.*, 16:417-424). Enzyme levels have been correlated to the severity of gum disease; C. M. Overall *et al* (1987), *J. Periodontal Res.*, 22:81-88.

Proteolytic processes have also been observed in the ulceration of the cornea following alkali burns (S. I. Brown *et al* (1969), *Arch. Ophthalmol.*, 81:370-373). Mercapto-containing peptides do inhibit the collagenase isolated from alkali-burned rabbit cornea (F. R. Burns *et al* (1989), *Invest. Ophthalmol.*, 30:1569-1575). Treatment of alkali-burned eyes or eyes exhibiting corneal ulceration as a result of infection with inhibitors of these metalloendoproteinases in combination with sodium citrate or sodium ascorbate and/or antimicrobials may be effective in preventing developing corneal degradation.

Stromelysin has been implicated in the degradation of structural components of the glomerular basement membrane (GBM) of the kidney, the major function of which is to restrict passage of plasma proteins into the urine (W. H. Baricos *et al* (1989), *Biochem. J.*, 254:609-612). Proteinuria, a result of glomerular disease, is excess protein in the urine caused by increased permeability of the GBM to plasma proteins. The underlying causes of the increased GBM permeability are unknown, but proteinases including stromelysin may play an important role in glomerular diseases. Inhibition of this enzyme may alleviate the proteinuria associated with kidney malfunction.

SUBSTITUTE SHEET (RULE 26)

It is suggested that inhibition of matrix metalloproteinase activity may prevent the rupturing of atherosclerotic plaques leading to coronary thrombosis. The tearing or rupture of atherosclerotic plaques is the most common event initiating coronary thrombosis. Destabilisation and degradation of the connective tissue matrix surrounding these plaques by proteolytic enzymes or cytokines released by infiltrating inflammatory cells has been proposed as a cause of plaque fissuring. Such tearing of these plaques can cause an acute thrombolytic event as blood rapidly flows out of the blood vessel. High levels of stromelysin RNA message have been found to be localised to individual cells in atherosclerotic plaques removed from heart transplant patients at the time of surgery (A. M. Henney *et al* (1991), Proc. Nat'l. Acad. Sci. USA, 88:8154-8158). Inhibition of stromelysin by these compounds may aid in preventing or delaying the degradation of the connective tissue matrix that stabilises the atherosclerotic plaques, thereby preventing events leading to acute coronary thrombosis.

It has been recently shown in a model of congestive heart failure (CHF) in the pig, that during CHF there are marked changes in the morphological structure of the heart. Ventricular dilation and wall thinning caused by changes to the extracellular matrix results in fewer collagen connections between cardiomyocytes and less total collagen. In such an instance a weaker force of contraction leads to an inefficient ventricular operation. It is believed that specific inhibitors of matrix metalloproteinases will play a key role in stabilising the extracellular matrix and therefore be important in the treatment and/or prevention of CHF.

It has recently been shown (WO 96/0240) that inhibitors of the matrix metalloproteinases, such as collagenase and stromelysin also inhibit the formation of human soluble CD23. CD23 is a 45kDa type II integral protein expressed on the surface of a variety of mature cells, including B and T lymphocytes, macrophages, NK cells, Langerhans cells, monocytes, eosinophils and platelets (Delespesse *et al*, Adv. Immunology, 49, 1991, 149; Grangette *et al*, J., Immunol, 143, 1989, 3580). Several activities have been ascribed to soluble CD23 in man, all of which involve

IgE regulation. Particular activities include:

- i) antigen presentation
- ii) IgE mediated eosinophil cytotoxicity

SUBSTITUTE SHEET (RULE 26)

- iii) B cell homing to lymph nodes and the spleen
- iv) downregulation of IgE synthesis

Thus, overall the excessive production of soluble CD23 has been implicated in the overproduction of IgE, the hallmark of allergic diseases such as extrinsic asthma, rhinitis, allergic conjunctivitis, eczema, atopic dermatitis and anaphylaxis (Sutton *et al*, *Nature*, 366, 1993, 421). Elevated levels of soluble CD23 have also been observed in the serum of patients with chronic B lymphocytic leukaemia (Safarti *et al*, *Blood*, 71, 1988, 94), and in the synovial fluid of patients with rheumatoid arthritis (Chomarat *et al*, *Arthritis and Rheumatism*, 36, 1993, 234).

It is therefore, a further objective of the present invention to provide compounds which inhibit the formation of human soluble CD23 for the production of a medicament for the treatment or prophylaxis of disorders such as allergy and autoimmune disease in which the overproduction of soluble CD23 is implicated, such as those described above.

Recent reports suggest that new enzymes of the MMP family also mediate the shedding of adhesion molecules such as the selectins, such as L-selectin. These soluble adhesion molecules are implicated in a number of diseases including cancer, autoimmunity and in the inflammatory response. It has been proposed that once cleaved, the selectin bind to particular ligands and this accounts for their biological activity. Thus, drugs that interfere with or prevent binding of the ligands to the selectins will be useful medicaments for treating a variety of the diseases described above. Therefore, it is a yet further objective of the present invention to provide compounds which inhibit the shedding of certain adhesion molecules and thus provide the production of a medicament for the treatment or prophylaxis of disorders such as cancer, autoimmune diseases or inflammatory diseases (such as inflammatory bowel disease and multiple sclerosis).

It is also believed that specific inhibitors of stromelysin and collagenase should be useful as birth control agents. There is evidence that expression of metalloproteinases, including stromelysin and collagenase, is observed in unfertilised eggs and zygotes and at further cleavage stages and increased at the blastocyst stage of fetal development and with endoderm differentiation (C. A. Brenner *et al* (1989), *Genes & Develop.*, 3:848-59). By analogy to tumour invasion, a blastocyst may

express metalloproteinases in order to penetrate the extracellular matrix of the uterine wall during implantation. Inhibition of stromelysin and collagenase during these early development processes should presumably prevent normal embryonic development and/or implantation in the uterus. Such intervention would constitute a novel method of birth control. In addition there is evidence that collagenase is important in ovulation processes. In this example, a covering of collagen over the apical region of the follicle must be penetrated in order for the ovum to escape. Collagenase has been detected during this process and an inhibitor has been shown to be effective in preventing ovulation (J. F. Woessner *et al* (1989), Steroids, 54:491-499). There may also be a role for stromelysin activity during ovulation (C. K. L. Too *et al* (1984), Endocrin., 115:1043-1050).

Collagenolytic and stromelysin activity have also been observed in dystrophic epidermolysis bullosa (A. Kronberger *et al* (1982), J. Invest. Dermatol., 79:208-211; D. Sawamura *et al* (1991), Biochem. Biophys. Res. Commun., 184:1003-8). Inhibition of metalloendoproteinases should limit the rapid destruction of connective components of the skin.

In addition to extracellular matrix comprising structural components, stromelysin can degrade other *in vivo* substrates including the inhibitors α_1 -proteinase inhibitor and may therefore influence the activities of other proteinases such as elastase (P. G. Winyard *et al* (1991), FEBS Letts., 279:1:91-94). Inhibition of the matrix metalloendoproteinases may potentiate the antiproteinase activity of these endogenous inhibitors.

From recent publications it is evident that several new enzymes of the MMP family have been identified, some of which may be important in disease. Collagenase 3, an enzyme found in breast carcinoma tissue may have utility in breast cancer (JMP Freije *et al* (1994), J. Biol. Chem., 269 (24): 16766-16773) and other disease states, such as arthritis, whilst MT-MMPs, other members of the MMP family have been shown to be key enzymes in the activation of gelatinase A (H Sato *et al* (1994), Nature, 370:61-65). Gelatinase A is an important enzyme in the growth and metastasis of tumours (such as defined above).

The degradation of β -Amyloid Precursor Protein (APP) has been shown to generate amyloid plaques, a major constituent of the senile plaques, found in patients

SUBSTITUTE SHEET (RULE 26)

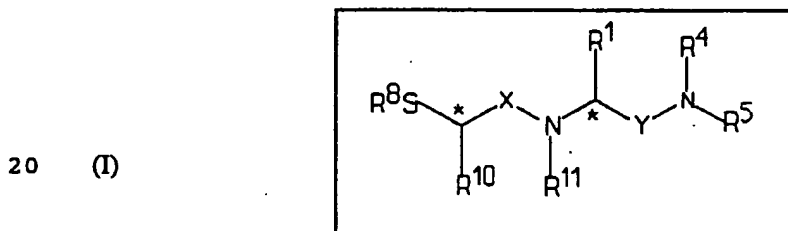
with Alzheimers Disease (AD). Two recent publications have identified metalloproteinase enzymes that cleave APP to the amyloid plaque (CR Abraham *et al* (1994), *Biochemistry*, **33**:192-199; G Huber *et al* (1994), *Biochem. Biophys. Res. Comm.*, **201** (1):45-53).

5 As appreciated by those of skill in the art, the significant proportion of homology between these new enzymes and other MMPs leads to the possibility that a compound that inhibits one enzyme may to some degree inhibit these new enzymes. Therefore, inhibitors encompassed in this invention may be useful in the diseases in which these new enzymes are implicated.

10 SUMMARY OF THE INVENTION

The invention encompasses novel compounds of formula (I) which are useful inhibitors of matrix metalloproteinases and/or TNF α mediated diseases including degenerative diseases (such as defined above) and certain cancers.

In a first aspect of the invention there is provided a compound of general
15 formula (I):



Wherein:

25 X and Y may be C=O or C=S and may be the same or different; Y may also be S(O)_m where m=1-2;

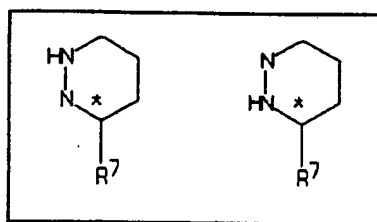
R¹ is a C₁₋₆ alkyl, C₂₋₆ alkenyl, aryl, C₁₋₆ alkyl-aryl, heteroaryl, C₁₋₆ alkyl-heteroaryl, cyclo(C₃₋₆) alkyl, C₁₋₆ alkyl-cyclo(C₃₋₆)alkyl, heterocyclo(C₄₋₆)alkyl, C₁₋₆ alkyl-heterocyclo(C₄₋₆)alkyl, C₁₋₆ alkyl-COR², or C₁₋₆ alkyl-AR³ group where A is O, NR³ or S(O)_n where n = 0-2 and R³ is H, C₁₋₄ alkyl, aryl, heteroaryl, C₁₋₄ alkyl-aryl or C₁₋₄ alkyl-heteroaryl; If A=NR³ the groups R³ may be the same or different.

R^2 is OR^4 or $N(R^4)_2$, where R^4 may be the same or different;

R^4 is H or C_{1-4} alkyl;

R^5 is aryl (optionally substituted with R^6), heteroaryl (optionally substituted with R^6), C_{1-4} alkyl-aryl (optionally substituted with R^6), C_{1-4} alkyl-heteroaryl (optionally substituted with R^6), C_{1-4} alkyl (substituted with R^{21}), cyclo(C_{3-6}) alkyl (optionally substituted with R^6), C_{1-4} alkyl-cyclo(C_{3-6})alkyl (substituted with R^6), heterocyclo(C_{4-6})alkyl (optionally substituted with R^6), or C_{1-4} alkyl-heterocyclo(C_{4-6})alkyl (optionally substituted with R^6);

NR^4R^5 may form a ring such as a pyrrolidine (optionally substituted with R^6), piperidine (optionally substituted with R^6), morpholine (optionally substituted with R^6) or piperazines of the type:



optionally substituted with R^6 at any available position.

R^6 is H, halogen, C_{1-6} alkyl, aryl, heteroaryl, OR^3 , $S(O)_nR^3$ where $n = 0-2$, NR^3R^7 , COR^9 , $SO_2N(R^3)_2$ where R^3 maybe the same or different, $CON(R^3)_2$ where R^3 maybe the same or different, amidine or guanidine;

R^7 is COR^9 , CO_2R^{19} , SO_2R^9 or $CO(NR^3)_2$ where R^3 maybe the same or different;

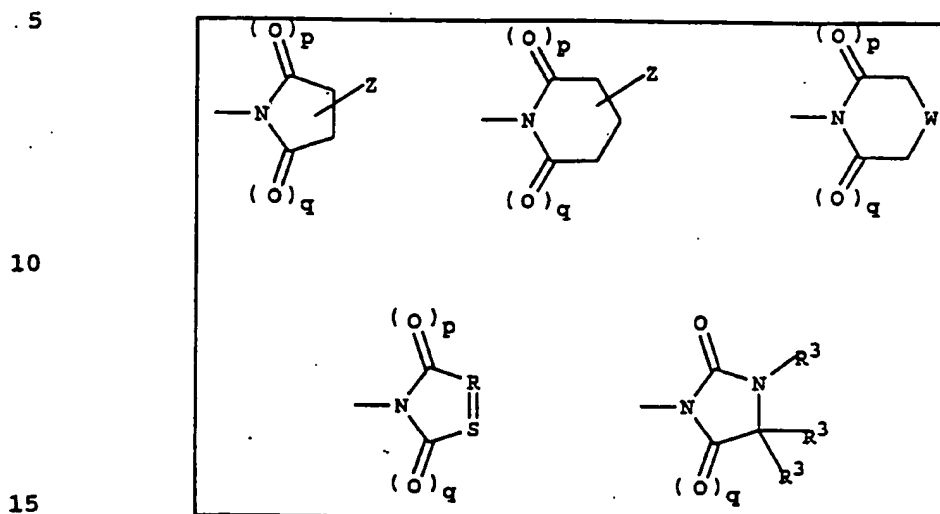
R^8 is H or the group COR^9 ;

R^9 is C_{1-4} alkyl, aryl, heteroaryl, C_{1-4} alkyl-aryl or C_{1-4} alkyl-heteroaryl;

R^{10} and R^{11} may be the same or different taken from the groups, H, C_{1-6} alkyl, (optionally substituted with R^{12}), aryl (optionally substituted with R^{12}), C_{1-6} alkyl-aryl (optionally substituted with R^{12}), heteroaryl (optionally substituted with R^{12}), C_{1-6} alkyl-heteroaryl (optionally substituted with R^{12}), cyclo(C_{3-6}) alkyl (optionally substituted with R^{12}), C_{1-6} alkyl-cyclo(C_{3-6})alkyl (optionally substituted with R^{12}), heterocyclo(C_{4-6})alkyl (optionally substituted with R^{12}) or C_{1-4} alkyl-heterocyclo(C_{4-6})alkyl (optionally substituted with R^{12});

11

R^{12} is SR^8 , COR^{13} , NR^3R^{14} the group AR^3 where A is O, NR^3 or $S(O)_n$ where $n = 0-2$, if $A=NR^3$ the groups R^3 may be the same or different, phthalimido or the groups:



p and q may be 0 or 1 and may be the same or different;

R and S may be CH or N and may be the same or different;

W may be O, $S(O)_n$ where $n = 0-2$ or NR^{15} ;

20 Z may be H or C_{0-4} alkyl- R^{18} and may be attached to any available position on the ring;

R^{13} is OR^{20} , $N(R^3)_2$ where R^3 maybe the same or different, C_{1-4} alkyl, aryl, C_{1-4} alkyl-aryl, heteroaryl or C_{1-4} alkyl-heteroaryl;

R^{14} may be any group defined in R^7 , SO_2R^{16} , or COR^{16} ;

25 R^{15} is H, C_{1-4} alkyl, COR^9 , CO_2R^{19} , $CON(R^3)_2$ where R^3 maybe the same or different or SO_2R^9 ;

R^{16} is C_{1-4} alkyl (optionally substituted with R^{17});

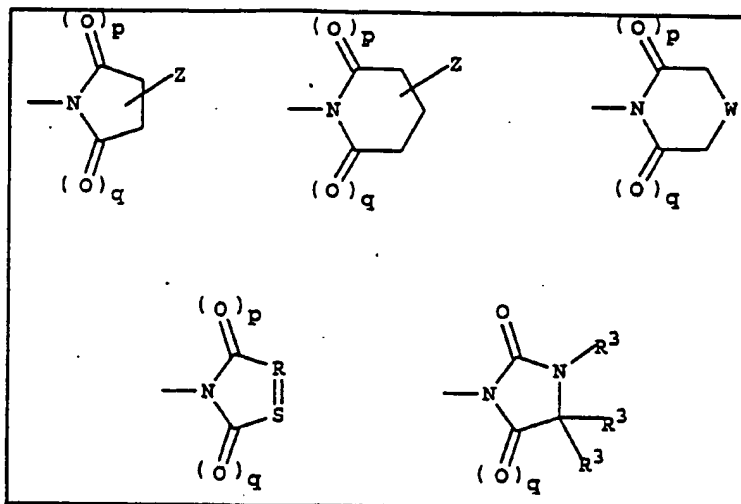
R^{17} may be CO_2R^3 , $CON(R^3)_2$ where R^3 maybe the same or different, $N(R^3)_2$ where R^3 maybe the same or different, SO_2R^9 or the groups:

30

SUBSTITUTE SHEET (RULE 26)

5

10



R^{18} is CO_2R^3 , $\text{CON}(R^3)_2$ where R^3 maybe the same or different, $\text{N}(R^3)_2$ where R^3 maybe the same or different, NHCO_2R^{19} , NHSO_2R^9 or NHCOR^9 ;

R^{19} is C_{1-4} alkyl, C_{1-4} alkyl-aryl or C_{1-4} alkyl-heteroaryl;

15 R^{20} is H, C_{1-4} alkyl, C_{1-4} alkyl-aryl or C_{1-4} alkyl-heteroaryl;

R^{21} is C_{1-4} alkyl, aryl, heteroaryl, NR^3R^7 , COR^9 , $\text{SO}_2\text{N}(R^3)_2$ where R^3 maybe the same or different, $\text{CON}(R^3)_2$ where R^3 maybe the same or different, amidine or guanidine;

and the salts, solvates and hydrates thereof.

20 Preferred compounds of the invention include those in which, independently or in any combination have:

X and Y is $\text{C}=\text{O}$

R^1 is a C_{1-6} alkyl or C_{1-6} alkyl- AR^3 group where A is O, NR^3 or $\text{S}(\text{O})_n$ where $n = 0-2$ and R^3 is H, C_{1-4} alkyl heteroaryl or aryl;

25 R^4 is H or C_{1-4} alkyl;

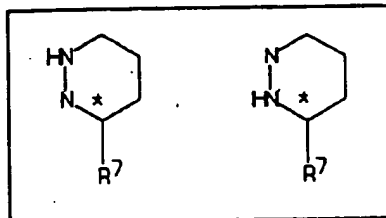
R^5 is aryl (optionally substituted with R^6), heteroaryl (optionally substituted with R^6), C_{1-4} alkyl-aryl (optionally substituted with R^6), C_{1-4} alkyl-heteroaryl (optionally substituted with R^6) or C_{1-4} alkyl-heterocyclo(C_{4-6})alkyl (optionally substituted with R^6);

30 R^6 is H, halogen, C_{1-6} alkyl, aryl, heteroaryl, AR^3 , NR^3R^7 , COR^9 , $\text{SO}_2\text{N}(R^3)_2$ where R^3 maybe the same or different, $\text{CON}(R^3)_2$ where R^3 maybe the same or different, amidine or guanidine;

SUBSTITUTE SHEET (RULE 26)

NR⁴R⁵ is a ring such as a pyrrolidine, piperidine, morpholine or piperazines of the type:

5



- 10 R⁷ is CO₂R¹⁹ or CONHR³ where R¹⁹ is H or C₁₋₄ alkyl;
 R⁸ is H or the group COR⁹;
 R⁹ is C₁₋₄ alkyl or aryl;
 R¹¹ is H;
 R¹⁰ is H, C₁₋₆ alkyl (optionally substituted with R¹²), C₁₋₆ alkyl-aryl (optionally substituted with R¹²) or C₁₋₆ alkyl-heteroaryl (optionally substituted with R¹²);
 15 R¹² is SR⁸, COR¹³, NR³R⁷, N(R³)₂, SO₂R⁹, phthalimido or succinimido;
 R¹³ is OR²⁰, N(R³)₂ where R³ maybe the same or different and R²⁰ is H or C₁₋₄ alkyl;

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms, for example those marked with an asterisk in formula (I). The presence of one or more of these
 20 asymmetric centres in a compound of formula (I) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

25 In the formulae herein, the ~ line is used at a potential asymmetric centre to represent the possibility of *R*- and *S*- configurations, the < line and the line to represent a unique configuration at an asymmetric centre.

As used in this specification, alone or in combination, the term "C₁₋₆ alkyl" refers to a straight or branched chain alkyl moiety having from one to six carbon
 30 atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like.

The term "C₁₋₄ alkyl" refers to a straight or branched chain alkyl moiety having from one to four carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl and the like.

5 The term "C₂₋₆ alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2- butenyl, 2- methyl-2-propenyl etc.

10 The term "cyclo (C₃₋₆) alkyl" refers to a saturated alicyclic moiety having from three to six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "cyclo (C₄₋₆) alkenyl" refers to an alicyclic moiety having from three to six carbon atoms and having in addition one double bond. This term would include for example cyclopentenyl or cyclohexenyl.

15 The term "heterocyclo (C₄₋₆) alkyl" refers to a saturated heterocyclic moiety having from three to six carbon atoms and one or more heteroatom from the group N, O, S and includes for example azetidyl, pyrrolidyl, tetrahydrofuranyl, piperidyl and the like.

20 There term "aryl" means an optionally substituted phenyl or naphthyl group with the substituent(s) being selected, for example, from halogen, trifluoromethyl, C₁₋₄ alkyl, alkoxy, phenyl and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

25 The terms "protected amino" and "protected carboxy" mean amino and carboxy groups which are protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzyloxycarbonyl, *tert*-butoxycarbonyl, acetyl or like groups, or in the form of a phthalimido or like group. A carboxyl group can be protected in the form of a readily cleavable ester such as the methyl, ethyl, benzyl or *tert*-butyl ester.

30 The term "heteroaryl" refers to aromatic ring systems of five to ten atoms or which at least one atom is selected from the group, O, N, or S and includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like.

Salts of compounds of formula (I) include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as

SUBSTITUTE SHEET (RULE 26)

hydrochlorides, hydrobromides, p-toluenesulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts may also be formed with bases. Such salts include salts derived from
5 inorganic or organic bases, for example alkali metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

When the "protected carboxy" group in compounds of the invention is an esterified carboxyl group, it may be a metabolically labile ester of formula CO_2R^{22}
10 where R^{22} may be an ethyl, benzyl, phenethyl, phenylpropyl, *a*- or *b*-naphthyl, 2,4-dimethylphenyl, 4-*tert*-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypentyl, 2,4,6-trimethylbenzyloxymethyl or pivaloyloxymethyl group.

Compounds of the general formula (I) may be prepared by any suitable
15 method known in the art and/or by the following processes, which itself forms part of the invention.

According to a second aspect of the invention, there is provided a process for preparing a compound of general formula (I) as defined above. It will be appreciated that where a particular stereoisomer of formula (I) is required, the
20 synthetic processes described herein may be used with the appropriate homochiral starting material and/or isomers may be resolved from mixtures using conventional separation techniques (eg. HPLC).

The compounds according to the invention may be prepared by the following process. In the description and formulae below the groups R^1 , R^2 , R^3 , R^4 , R^5 , R^6 ,
25 R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R, S, W, X, Y and Z are as defined above, except where otherwise indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances,
30 removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in

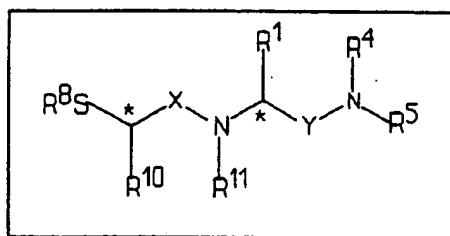
the art. For specific details see "Protective Groups in Organic Synthesis", Wiley Interscience, T W Greene, PGM. Wuts.

The process required for preparing compounds of general formula (I) comprises of:

- 5 deprotecting (for example by hydrolysis) a compound of general formula (II)

10

(II)



Wherein R^8 represents a suitable protecting group (eg *tert*-butyl, trityl, benzoyl or acetate).

15

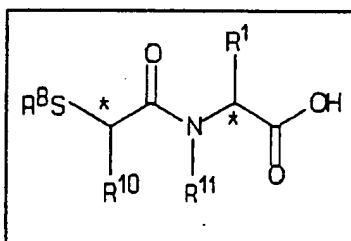
It will be appreciated that where a particular stereoisomer of formula (I) is required, this may be obtained by conventional resolution techniques such as high performance liquid chromatography. Where desired, however, appropriate homochiral starting materials may be used in the coupling reaction to yield a particular stereoisomer of formula (I). This is exemplified below.

20

When X and Y are C=O, intermediates of general formula (II) may be prepared by coupling an acid of formula (III)

25

(III)

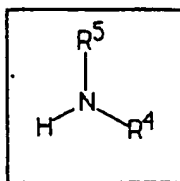


Wherein R^1 , R^{10} and R^{11} are as defined above, or an active derivative thereof, with an amine of formula (IV)

30

17

(IV)



5

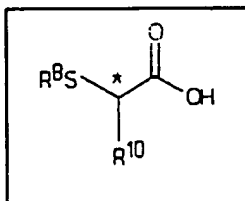
Where R^4 and R^5 are defined previously.

Amines of formula (IV) may be commercially available or can be readily obtained from commercially available starting materials using methods known to those skilled in the art.

10 Active derivatives of acids of formula (III) include for example acid anhydrides or acid halides, such as acid chlorides.

The coupling reaction may be performed using standard conditions for amination reactions of this type. Thus, the reaction may be achieved in a solvent, for example an inert organic solvent such as an ether, eg. a cyclic ether such as tetrahydrofuran, an amide eg. a substituted amide such as dimethylformamide, or a
15 halogenated hydrocarbon such as dichloromethane at a low temperature eg. -30°C to ambient temperature, such as -20°C to 0°C , optionally in the presence of as base, eg. an organic base such as an amine, eg. triethylamine or a cyclic amine such as *N*-methylmorpholine. Where an acid of formula (III) is used, the reaction may
20 additionally be performed in the presence of a condensing agent, for example a diimide such as *N,N'*-dicyclohexylcarbodiimide, advantageously in the presence of a triazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate for example ethylchloroformate, prior to reaction with the amine of formula (IV).

25 The acid of general formula (III) may be prepared by coupling an acid of formula (V), or an active derivative thereof



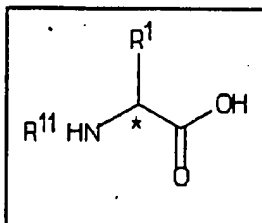
30

(V)

With an amine of formula (VI)

5

(VI)

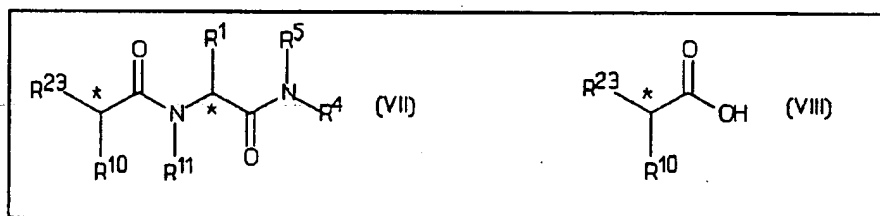


followed by removal of any protecting groups.

Active derivatives of acids for formula (V) include for example acid anhydrides or acid halides such as acid chlorides as outlined earlier.

α -Thioacetic acids and amino acids and their derivatives such as depicted by general formulae (V) and (VI) respectively can be obtained in optically pure or racemic form. In the homochiral form they provide asymmetric building blocks for the enantiospecific synthesis of compounds of general formula (I). Many of these derivatives can be readily obtained from commercially available starting materials using methods known to those skilled in the art. (See "The Practice of Peptide Synthesis" by M. Bodanszky et al, Springer Verlag, New York, 1984, P. L. Durette, WO92/21360).

As a further extension to the present invention compounds of general formula (II) or (V) may be prepared by nucleophilic substitution of compounds of general formula (VII) or (VIII) respectively.



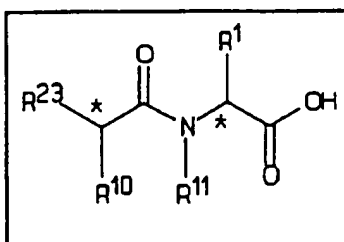
Wherein R^{23} represents a suitable leaving group (eg. a halogen such as bromide, or an alkylsulphonate ester such as methanesulphonate) with a thiol of general formula (IX)

SUBSTITUTE SHEET (RULE 26)

Wherein R⁸ represents a suitable protecting group (eg. *tert* butyl, trityl, benzoyl or acetate), using standard conditions known to those skilled in the art as exemplified by C.Campion *et al*, WO 90/9005719.

Thiols of general formula (IX) may be obtained from commercially available starting materials using methods known to those skilled in the art. Many thiols of general formula (IX) are also commercially available.

Compounds of general formula (VII) may be prepared by coupling an acid of general formula (X)



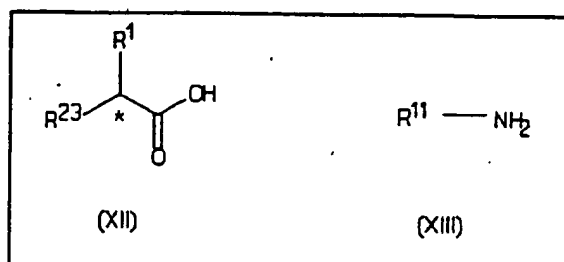
(X)

Wherein R²³, R¹⁰ and R¹¹ are as defined above (or suitably protected versions thereof) or an active derivative thereof, with an amine of formula (IV) using similar coupling conditions to those described for the preparation of compounds of formula (II).

Carboxylic acids of the structure depicted in formulae (VIII) and (X) can be obtained in chiral or racemic form. Many of these derivatives can be readily obtained from commercially available starting materials using methods known to those skilled in the art (see C.Campion *et al* WO 90/9005719).

Where R^{11} is not H and amino acids of general formula (VI) are required, these may be prepared by the nucleophilic displacement of an alkylating agent of formula (XII) with an amine of formula (XIII)

5



10

wherein R^{11} and R^{23} have been defined previously.

Intermediates of formula (XII) may be prepared from amino acids of general formula (VI) by diazotisation under appropriate conditions.

Amines of formula (XIII) may be commercially available or can be readily obtained from commercially available starting materials using methods known to those skilled in the art.

Compounds of formula (I) may also be prepared by interconversion of other compounds of formula (I). Thus, for example, a compound of formula (I) wherein R^1 is a C_{1-6} alkyl group may be prepared by hydrogenation (using palladium on carbon in suitable solvent, such as an alcohol - eg ethanol) of a compound of formula (I) wherein R^1 is a C_{2-6} alkenyl group. A further example would include a compound of formula (I) wherein R^8 is a group $R^9 CO$ may be prepared by acylation (using a suitable acid chloride $R^9 COCl$, in the presence of a base such as a triethylamine in a suitable solvent, such as a chlorinated solvent - eg dichloromethane) of a compound of formula (I) wherein R^8 is H.

25

Also compounds where X and Y are $C=S$ may be prepared by thioamidation, for instance with Lawesson's Reagent, of compounds where X and Y are $C=O$.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

30

SUBSTITUTE SHEET (RULE 26)

The compounds according to the invention exhibit *in vitro* inhibiting activities with respect to stromelysin, collagenase and gelatinase. Compounds according to the invention also exhibit *in vitro* inhibition of TNF release. The activity and selectivity of the compounds may be determined by use of the appropriate enzyme inhibition test, for example as described in Example A hereinafter.

This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from disorders or diseases which can be attributed to stromelysin as previously described, and more specifically, a method of treatment involving the administration of the matrix metalloproteinase inhibitors of formula (I) as the active constituents.

Accordingly, the compounds of formula (I) can be used among other things in the treatment of osteoarthritis and rheumatoid arthritis, and in diseases and indications resulting from the over-expression of these matrix metalloproteinases such as found in certain metastatic tumour cell lines.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine since they are active as inhibitors of TNF and MMPs. Accordingly in another aspect, this invention concerns:

a method of management (by which is meant treatment or prophylaxis) of disease or conditions mediated by TNF and/or MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof; and

a compound of formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs; and

the use of a compound of formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs.

The disease or conditions referred to above include inflammatory diseases, autoimmune diseases cancer, cardiovascular diseases, diseases involving tissue breakdown such as rheumatoid arthritis, osteoarthritis, osteoporosis,

neurodegeneration, Alzheimer's disease, atherosclerosis, congestive heart failure, stroke, vasculitis, Crohn's disease, ulcerative colitis, multiple sclerosis, periodontitis, gingivitis and those involving tissue breakdown such as bone resorption, haemorrhage, coagulation, acute phase response, cachexia and anorexia, acute infections, HIV infections, fever, shock states, graft versus host reactions, dermatological conditions, surgical wound healing, psoriasis, atopic dermatitis, epidermolysis bullosa, tumour growth, angiogenesis and invasion by secondary metastases, ophthalmological disease, retinopathy, corneal ulceration, reperfusion injury, migraine, meningitis, asthma, rhinitis, allergic conjunctivitis, eczema and anaphylaxis.

For the treatment of rheumatoid arthritis, osteoarthritis, and in diseases and indications resulting from the over-expression of matrix metalloendoproteinases such as found in certain metastatic tumour cell lines or other diseases mediated by the matrix metalloendoproteinases or increased TNF production, the compounds of formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the treatment of humans.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium

carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the US Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules where in the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening

agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

5 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified, for example sweetening, flavouring and colouring agents, may also be present.

10 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soya bean,
15 lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

 Syrups and elixirs may be formulated with sweetening agents, for example
20 glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which
25 have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed
30 as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

SUBSTITUTE SHEET (RULE 26)

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc containing the compounds of Formula (I) are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above- indicated conditions (about 2.5 mg to about 7 gms per patient per day). for example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 gms per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following non-limiting Examples are intended to illustrate the preparation of compounds of Formula (I), and as such are not intended to limit the invention as set forth in the claims. In the Examples, the following abbreviations are used:

RT Room temperature
DCC Dicyclohexylcarbodiimide

EDC 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride

TNF α Tumour necrosis factor α

LPS Lipopolysaccharide

ELISA Enzyme linked immunosorbent assay

5 Intermediate 1 5-Phthalimidopentanoic acid

N-Carboethoxyphthalimide (17.2g, 78.6mmol) was added in one portion to a vigorously stirred solution of 5-aminovaleric acid (9.26g, 79.1mmol) and sodium carbonate (8.45g, 79.9mmol) in water (300ml) at RT. The mixture was stirred until essentially all the solid material had dissolved (30 min), then it was filtered. The
10 filtrate was acidified to pH1 with 6M hydrochloric acid (ca. 20ml) and the white precipitate was collected by filtration and washed thoroughly with water (150ml). The solid was dried in air, then *in vacuo* to give the title compound as a colourless solid (13.5g, 69%).

¹H NMR (250 MHz; CDCl₃, Ref., TMS) δ 1.6-1.8 (4H, m), 2.20 (2H, t), 3.85
15 (2H, t), 7.70-7.75 (2H, m), 7.85-7.95 (2H, m) and 10.2 (1H, br s).

Intermediate 2 (RS) 2-Bromo-5-phthalimidopentanoic acid

Intermediate 1 (5.0g, 20.2mmol) and thionyl chloride (10ml) were heated together at 65°C for 30 min. *N*-Bromosuccinimide (5.4g, 30.3mmol) and further thionyl chloride (10ml) were added, plus 48% aqueous HBr (1 drop). The solution
20 was heated at 70-80°C for 4h. Further *N*-Bromosuccinimide (2.7g, 15.2mmol) was added and the mixture was heated at 70-80°C for another 2h. Excess thionyl chloride was removed by evaporation under reduced pressure and the oily residue diluted with dry tetrahydrofuran (200 ml) and water (200ml). The mixture was then treated cautiously with solid sodium bicarbonate to pH 7-8 then stirred overnight at
25 RT. Excess tetrahydrofuran was removed *in vacuo* and the residue washed with dichloromethane (3x300ml). The aqueous portion was then cautiously acidified to pH 1 using 6M hydrochloric acid and extracted with dichloromethane (4x200ml). The combined extracts were then washed with water (2x400ml) and brine (400ml), dried (MgSO₄) and evaporated *in vacuo* to provide the product (4.7g, 71%) as a
30 fawn solid.

TLC R_f 0.47 (EtOAc)

Intermediate 3 (RS) 2-Acetylsulphanyl-5-phthalimidopentanoic acid

A solution of intermediate 2 (3.0g, 9.2mmol) in methanol (30ml) was treated with potassium thioacetate (1.05g, 9.2mmol) and the mixture stirred at RT overnight. The mixture was evaporated *in vacuo*, the residue dissolved in dichloromethane (100ml) then the solution washed with water (2x50ml), dried (MgSO₄) and evaporated *in vacuo* to provide the product (2.4g, 81%) as a pale yellow foam.

TLC R_f 0.43 (EtOAc)

Intermediate 4 2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucine 1,1-dimethylethyl ester

EDC (3.64g, 19mmol) was added to a stirred mixture of L-leucine 1,1-dimethylethyl ester (3.93g, 17.6mmol), *N*-hydroxybenzotriazole (2.62g, 19.4mmol), triethylamine (2.51ml, 18mmol) and intermediate 3 (5.94g, 18.5mmol) in dry tetrahydrofuran (200ml). The mixture was stirred overnight then the solvent removed *in vacuo* and the residue partitioned between water (100ml) and ethyl acetate (100ml). The aqueous portion was then extracted with ethyl acetate (2x50ml), the combined extracts washed with water (2x100ml) and brine (100ml), dried (MgSO₄) and evaporated *in vacuo* to a colourless oil.

Purification by column chromatography eluting with hexane/ethyl acetate (2:1) provided the title compound (6.6g, 77%) as a white solid, a 1:1 mixture of diastereoisomers.

TLC R_f 0.42 (EtOAc/Hexane (1:1))

Intermediate 5 2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucine

Trifluoroacetic acid (9.0ml, 115mmol) was added to a stirred solution of intermediate 4 (3.0g, 6.1mmol) in dry dichloromethane (40ml) and the mixture stirred at RT overnight. The mixture was concentrated *in vacuo* and the excess trifluoroacetic acid removed by azeotrope with heptane to provide the title compound (2.48g, 94%) as a colourless foam, a 1:1 mixture of diastereoisomers.

TLC R_f 0.42 (EtOAc/Hexane (3:2))

Intermediate 6 (3S)-(1,1-Dimethylethyloxy)carbonyl-hexahydropyridazine-3-carboxylic acid *N*-methyl amide

Was prepared according to the method of C.E. Adams, *et al*, *Synth. Commun.*, 1988, 18, 2225.

Example 1 2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucin *N*-(2-phenylethyl)amide

A solution of intermediate 5 (400mg, 0.92mmol), *N*-hydroxybenzotriazole (137mg, 1.01mmol) and phenethylamine (116ml, 0.92mmol) in dry tetrahydrofuran (20ml) was treated at RT with EDC (194mg, 1.01mmol) and the mixture stirred overnight. The mixture was diluted with ethyl acetate (80ml) and the resulting solution washed with 2M hydrochloric acid (50ml), 8% aqueous sodium bicarbonate (50ml), water (50ml) and brine (50ml), dried (MgSO₄) and evaporated *in vacuo* to provide a colourless oil.

Purification by column chromatography eluting with 3% methanol in dichloromethane furnished the title compound (440mg, 89%) as a white solid.

TLC R_f 0.49 (3% MeOH-CH₂Cl₂)

C₂₉H₃₅N₃O₅S [537.7], MH⁺ 538

Similarly prepared were:

Example 2 2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucine *N*-(2-phenylmethyl)amide

From intermediate 5 and benzylamine, as a white solid (460mg, 76%).

TLC R_f 0.35 (5% MeOH-CH₂Cl₂)

C₂₈H₃₃N₃O₅S [523.7], MH⁺ 524

Example 3 2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(~~H~~indol-3-yl)ethyl]amide

From intermediate 5 and tryptamine, as a pale yellow solid (1.36g, 52%).

TLC R_f 0.27 (5% MeOH-CH₂Cl₂)

C₃₁H₃₆N₄O₅S [576.7], MH⁺ 577

Example 4 2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(5-methoxy-1H-indol-3-yl)ethyl]amide

From intermediate 5 and 5-methoxytryptamine, as a pale yellow solid (447mg, 67%).

TLC R_f 0.40 (5% MeOH-CH₂Cl₂)

C₃₂H₃₈N₄O₆S [606.7], MH⁺ 607

Example 5 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(6-methoxy-1H-indol-3-yl)ethyl]amide

From intermediate 5 and 6-methoxytryptamine, as a pale yellow solid (333mg, 50%).

5 TLC R_f 0.42 (5% MeOH-CH₂Cl₂)

C₃₂H₃₈N₄O₆S [606.7], MH⁺ 607

Example 6 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(2-pyridyl)ethyl]amide

From intermediate 5 and 2-pyridylethylamine, as a white solid (347mg, 63%).

10 TLC R_f 0.35 (5% MeOH-CH₂Cl₂)

C₂₈H₃₄N₄O₅S [538.7], MH⁺ 539

Example 7 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(methoxycarbonyl)ethyl]amide

15 From intermediate 5 and 2-aminopropanoic acid methyl ester, as a white solid (355mg, 53%).

TLC R_f 0.45 (5% MeOH-CH₂Cl₂)

C₂₅H₃₃N₃O₅S [519.6], MH⁺ 520

The following examples were also prepared by the method outlined above:

20 **Example 8** 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[4-morpholino]amide

Example 9 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[(4-methyl-3-oxo)piperazino]amide

25 **Example 10** 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[(4-acetyl)piperazino]amide

Example 11 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[(2-acetylamino)ethyl]amide

Example 12 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(4-morpholino)ethyl]amide

30 **Example 13** 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[3-(1-imidazolyl)propyl]amide

Example 14 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

Example 15 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(1-oxo-1-phenyl)ethyl]amide

5 **Example 16** 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[4-(sulphonamido)phenyl]amide

Example 17 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-(2-phenylethyl)amide

10 **Example 18** 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-[4-morpholino]amide

Example 19 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-[4-methoxyphenyl]amide

Also prepared was:

15 **Example 20** 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-[(3*S*)-hexahydropyridazine]-3-carboxylic acid *N*-methyl amide

From intermediate 6, as a colourless foam (45%) after removal of the *tert*-butoxycarbonyl group with trifluoroacetic acid under standard conditions.

TLC R_f 0.38 (5% MeOH-CH₂Cl₂)

20 **Example 21** 2-Sulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(2-phenylmethyl)amide

A solution of example 2 (299mg, 0.57mmol) in dry methanol (15ml) was treated at RT with concentrated ammonia solution (1.0ml) and the mixture stirred for 2h. The solvent was removed in vacuo and the residue purified by column chromatography eluting with 3% methanol in dichloromethane to provide the title
25 compound (228mg, 83%) as a white solid.

TLC R_f 0.27 (5% MeOH-CH₂Cl₂)

C₂₆H₃₁N₃O₄S [481.6], MH⁺ 482

Similarly prepared were:

30 **Example 22** 2-Sulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(2-phenylethyl)amide

From example 1, as a white solid (247mg, 95%)

TLC R_f 0.31 (5% MeOH-CH₂Cl₂)

C₂₇H₃₃N₃O₄S [495.7], MH⁺ 496

SUBSTITUTE SHEET (RULE 26)

Example 23 2-Sulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(1H-indol-3-yl)ethyl]amide

From example 3, as a pale yellow solid (120mg, 45%).

TLC R_f 0.55 (5% MeOH-CH₂Cl₂)

5 C₂₅H₃₄N₄O₄S [534.7], MH⁺ 535

Example 24 2-Sulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(5-methoxy-1H-indol-3-yl)ethyl]amide

From example 4, as a near white solid (150mg, 53%).

TLC R_f 0.35 (5% MeOH-CH₂Cl₂)

10 C₃₀H₃₆N₄O₅S [564.7], MH⁺ 565

Example 25 2-Sulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(6-methoxy-1H-indol-3-yl)ethyl]amide

From example 5, as a pale yellow solid (160mg, 56%).

TLC R_f 0.42 (5% MeOH-CH₂Cl₂)

15 C₃₀H₃₆N₄O₅S [564.7], MH⁺ 565

Example 26 2-Sulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(2-pyridyl)ethyl]amide

From example 6, as a white solid (155mg, 69%).

TLC R_f 0.35 (5% MeOH-CH₂Cl₂)

20 C₂₆H₃₂N₄O₄S [496.6], MH⁺ 497

Example 27 2-Sulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(methoxycarbonyl)ethyl]amide

From example 7, as a white solid (110mg, 58%).

TLC R_f 0.43 (5% MeOH-CH₂Cl₂)

25 C₂₃H₃₁N₃O₆S [477.5], MH⁺ 478

Example 28 2-Sulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-(2-phenylethyl)amide

From example 17, as a white solid (428mg, 88%).

TLC R_f 0.47 (5% MeOH-CH₂Cl₂)

30 **Example 29** 2-Sulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-[4-morpholino]amide

From example 18, as a white solid (367mg, 85%).

TLC R_f 0.42 (5% MeOH-CH₂Cl₂)

Example 30 2-Sulphanyl-5-phthalimidopentanoyl-L-(S-methyl)cysteinyl
N-[4-methoxyphenyl]amide

From example 19, as a white solid (300mg, 80%).

5 TLC R_f 0.47 (5% MeOH-CH₂Cl₂)

Example 31 2-Sulphanyl-5-phthalimidopentanoyl-L-(S-methyl)cysteinyl N-[(3S)-
hexahydropyridazine]-3-carboxylic acid N-methyl amide

From example 20, as a white solid (20mg, 36%).

TLC R_f 0.37 (5% MeOH-CH₂Cl₂)

10 **Example A**

Collagenase inhibition activity

The potency of compounds of general formula (I) to act as inhibitors of collagenase was determined by the procedure of Cawston and Barrett, (Anal. Biochem., 99:340-345, 1979) whereby a 1mM solution of the inhibitor being tested or dilutions thereof was incubated at 37°C for 16 hours with collagen and collagenase (buffered with 50 mM Tris, pH 7.6 containing 5 mM CaCl₂, 0.05% Brij 35, 60 mM NaCl and 0.02% NaN₃). The collagen was acetylated ³H or ¹⁴C-collagen prepared by the method of Cawston and Murphy (Methods in Enzymology, 80:711, 1981). The choice of radiolabel did not alter the ability of collagenase to degrade the collagen substrate. The samples were centrifuged to sediment undigested collagen and an aliquot of the radioactive supernatant removed for assay on a scintillation counter as a measure of hydrolysis. The collagenase activity in the presence of 1mM inhibitor, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the results reported as that inhibitor concentration effecting 50% inhibition of the collagenase (IC₅₀).

Example B

Stromelysin inhibition activity

The potency of compounds of general formula (I) to act as inhibitors of stromelysin was determined using the procedure of Nagase et al (Methods in Enzymology Vol 254, 1994), whereby a 0.1 mM solution of the inhibitor being tested or dilutions thereof was incubated at 37°C for 16 hours with stromelysin and ³H transferrin (buffered with 50 mM Tris, pH 7.6 containing 10 mM CaCl₂, 150M

NaCl, 0.05% Brij, 35, and 0.02% NaN₃). The transferrin was carboxymethylated with ³H iodoacetic acid. The stromelysin activity in the presence of 1 mM, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the results reported as that inhibitor concentration effecting 50% inhibition of the stromelysin (IC₅₀)

Example C

Gelatinase inhibition activity

The potency of the compounds of general formula (I) to act as inhibitors of gelatinase was determined using the procedure of Harris & Krane (Biochem Biophys. Acta, 258:566 - 576, 1972), whereby a 1 mM solution of the inhibitor being tested or dilutions thereof was incubated at 37°C for 16 hours with gelatinase and heat denatured ³H or ¹⁴C-acetylated collagen (buffered with 50 mM Tris, pH 7.6 containing 5 mM CaCl₂, 0.05% Brij 35 and 0.02% NaN₃). The ³H or ¹⁴C gelatin was prepared by denaturing ³H or ¹⁴C-collagen produced according to the method of Cawston and Murphy (Methods in Enzymology, 80:711, 1981) by incubation at 60°C for 30 minutes. Undigested gelatin was precipitated by addition of trichloroacetic acid and centrifugation. The gelatinase activity in the presence of 1 mM, or dilution thereof, was compared to the activity in a control devoid of inhibitor and results reported as that inhibitor concentration effecting 50% inhibition of the gelatinase (IC₅₀).

Example D

MMP Inhibition Activity-Fluorimetric Assay

The potency of compounds of general formula (I) to act as inhibitors of collagenase-1 (MMP-1), collagenase-2 (MMP-8), gelatinase-A (MMP-2), gelatinase-B (MMP-9) and stromelysin-1 (MMP-3) was determined using the following procedure: Inhibitors are dissolved in dimethylsulphoxide containing 0.02% b-mercaptoethanol and serial dilutions are prepared. Activated enzyme is incubated in assay buffer containing 50mM Tris, pH 7.4, 5mM CaCl₂, 0.002% NaN₃ and Brij 35 in the presence and absence of inhibitor. Samples are preincubated at 37°C for 15 minutes before the addition of the fluorimetric substrate (Mca-Pro-Leu-Dpa-Ala-Arg-NH₂) to a final concentration of 10mM. The assay is incubated for 90 minutes at 37°C and then read in a Fluoroscan II at I_{ex} (355nm) and I_{em} (460nm).

The enzyme activity was compared to activity in a control devoid of inhibitor and the results reported as that inhibitor concentration effecting 50% inhibition of the stromelysin (IC_{50}).

Example E

5 Inhibition of $TNF\alpha$ production

The potency of the compounds of general formula (I) to act as inhibitors of the production of $TNF\alpha$ was determined using the following procedure. A 1mM solution of the inhibitor being tested or dilutions thereof was incubated at 37° C in an atmosphere of 5% CO_2 with THP-1 cells (human monocytes) suspended in RPMI
10 1640 medium and 20 μ M β -mercaptoethanol at a cell density of 1×10^6 /ml and stimulated with 5 μ g/ml final concentration of LPS. After 18 hours the supernatant is assayed for the levels of $TNF\alpha$ using a commercially available ELISA kit (R & D Systems).

The activity in the presence of 0.1mM inhibitor or dilutions thereof was
15 compared to activity in a control devoid of inhibitor and results reported as that inhibitor concentration effecting 50% inhibition of the production of $TNF\alpha$.

Example F

Adjuvant arthritic rat model

Compounds of general formula (I) were evaluated in an adjuvant arthritis
20 model in the rat based on the methods employed by B.B. Newbould (1963), Br.J.Pharmacol, 21, 127-136 and C.M. Pearson and F.D. Wood (1959), Arthritis Rheum, 2, 440-459. Briefly male Wistar rats (180-200g) were injected at the base of the tail with Freund's adjuvant. Twelve days later the responding animals were randomised into experimental groups. Compounds of general formula (I) were dosed
25 either orally as a suspension in 1% methyl cellulose or intraperitoneally in 0.2% carboxymethylcellulose from day 12 to the end of the experiment on day 22. Hind paw volumes were measured every two days from day 12 onwards and X-rays were taken of the hind feet on completion of the experiment. Results were expressed as the percent increase of foot volume over day 12 values.

Example G**Mouse ovarian carcinoma xenograft model**

Compounds of general formula (I) were evaluated in an ovarian carcinoma xenograft model of cancer, based on that described by B. Davies et al (1993), Cancer Research, 53, 2087-2091. This model, in brief, consists of inoculating female nu/nu mice with 1×10^9 OVCAR3-icr cells into the peritoneal cavity. Compounds of general formula (I) are administered by the oral route as a suspension in 1% methyl cellulose or intraperitoneally as a suspension in phosphate buffered saline in 0.01% Tween-20. At the conclusion of the experiment (4-5 weeks) the number of peritoneal cells are counted and any solid tumour deposits weighed. In some experiments tumour development is monitored by measurement of tumour specific antigens.

Example H**Rat mammary carcinoma model**

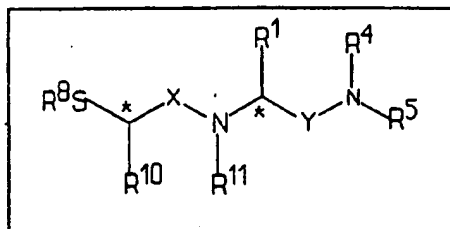
Compounds of general formula (I) were evaluated in a HOSP.1 rat mammary carcinoma model of cancer (S.Eccles et al (1995), Cancer Research, in press). This model consists of the intravenous inoculation of female CBH/cbi rats with 2×10^4 tumour cells into the jugular vein. Compounds of general formula (I) are administered by the oral route as a suspension in 1% methyl cellulose or intraperitoneally as a suspension in phosphate buffered saline in 0.01% Tween-20. At the conclusion of the experiment (4-5 weeks) the animals were killed, the lungs were removed and individual tumours counted after 20 hours fixation in Methacarn.

CLAIMS

1. Compounds of general formula (I):

5

(I)



10 Wherein:

X and Y may be C=O or C=S and may be the same or different; Y may also be S(O)_m where m=1-2;

R¹ is a C₁₋₆ alkyl, C₂₋₆ alkenyl, aryl, C₁₋₆ alkyl-aryl, heteroaryl, C₁₋₆ alkyl-heteroaryl, cyclo(C₃₋₆) alkyl, C₁₋₆ alkyl-cyclo(C₃₋₆)alkyl, heterocyclo(C₄₋₆)alkyl, C₁₋₆ alkyl-heterocyclo(C₄₋₆)alkyl, C₁₋₆ alkyl-COR², or C₁₋₆ alkyl-AR³ group where A is O, NR³ or S(O)_n where n = 0-2 and R³ is H, C₁₋₄ alkyl, aryl, heteroaryl, C₁₋₄ alkyl-aryl or C₁₋₄ alkyl-heteroaryl; If A=NR³ the groups R³ may be the same or different.

R² is OR⁴ or N(R⁴)₂ where R⁴ may be the same or different;

R⁴ is H or C₁₋₄ alkyl;

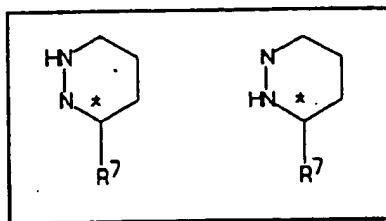
20 R⁵ is aryl (optionally substituted with R⁶), heteroaryl (optionally substituted with R⁶), C₁₋₄ alkyl-aryl (optionally substituted with R⁶), C₁₋₄ alkyl-heteroaryl (optionally substituted with R⁶), C₁₋₄ alkyl (substituted with R²¹), cyclo(C₃₋₆) alkyl (optionally substituted with R⁶), C₁₋₄ alkyl-cyclo(C₃₋₆)alkyl (substituted with R⁶), heterocyclo(C₄₋₆)alkyl (optionally substituted with R⁶), or C₁₋₄ alkyl-heterocyclo(C₄₋₆)alkyl (optionally substituted with R⁶);

25 NR⁴R⁵ may form a ring such as a pyrrolidine (optionally substituted with R⁶), piperidine (optionally substituted with R⁶), morpholine (optionally substituted with R⁶) or piperazines of the type:

30

SUBSTITUTE SHEET (RULE 26)

37



5

optionally substituted with R^6 at any available position.

R^6 is H, halogen, C_{1-6} alkyl, aryl, heteroaryl, OR^3 , $S(O)_nR^3$ where $n = 0-2$, NR^3R^7 , COR^9 , $SO_2N(R^3)_2$ where R^3 maybe the same or different, $CON(R^3)_2$ where R^3 maybe the same or different, amidine or guanidine;

10 R^7 is COR^9 , CO_2R^{10} , SO_2R^9 or $CO(NR^3)_2$ where R^3 maybe the same or different;

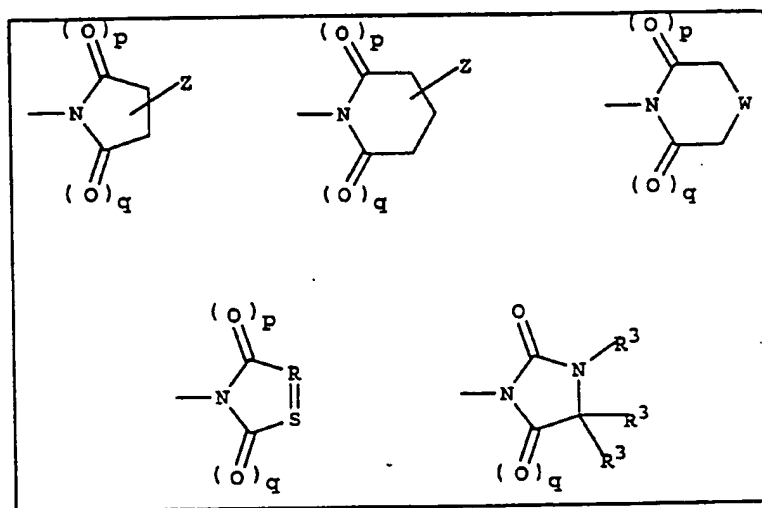
R^8 is H or the group COR^9 ;

R^9 is C_{1-4} alkyl, aryl, heteroaryl, C_{1-4} alkyl-aryl or C_{1-4} alkyl-heteroaryl;

R^{10} and R^{11} may be the same or different taken from the groups, H, C_{1-6} alkyl, (optionally substituted with R^{12}), aryl (optionally substituted with R^{12}), C_{1-6} alkyl-aryl

15 (optionally substituted with R^{12}), heteroaryl (optionally substituted with R^{12}), C_{1-6} alkyl-heteroaryl (optionally substituted with R^{12}), cyclo(C_{3-6}) alkyl (optionally substituted with R^{12}), C_{1-6} alkyl-cyclo(C_{3-6}) alkyl (optionally substituted with R^{12}), heterocyclo(C_{4-6}) alkyl (optionally substituted with R^{12}) or C_{1-4} alkyl-heterocyclo(C_{4-6}) alkyl (optionally substituted with R^{12});

20 R^{12} is SR^8 , COR^{13} , NR^3R^{14} the group AR^3 where A is O, NR^3 or $S(O)_n$ where $n = 0-2$, if $A=NR^3$ the groups R^3 may be the same or different, phthalimido or the groups:



25

30

SUBSTITUTE SHEET (RULE 26)

p and q may be 0 or 1 and may be the same or different;

R and S may be CH or N and may be the same or different;

W may be O, S(O)_n where n = 0-2 or NR¹⁵;

5 Z may be H or C₀₋₄ alkyl-R¹⁸ and may be attached to any available position on the ring;

R¹³ is OR²⁰, N(R³)₂ where R³ maybe the same or different, C₁₋₄ alkyl, aryl, C₁₋₄ alkyl-aryl, heteroaryl or C₁₋₄ alkyl-heteroaryl;

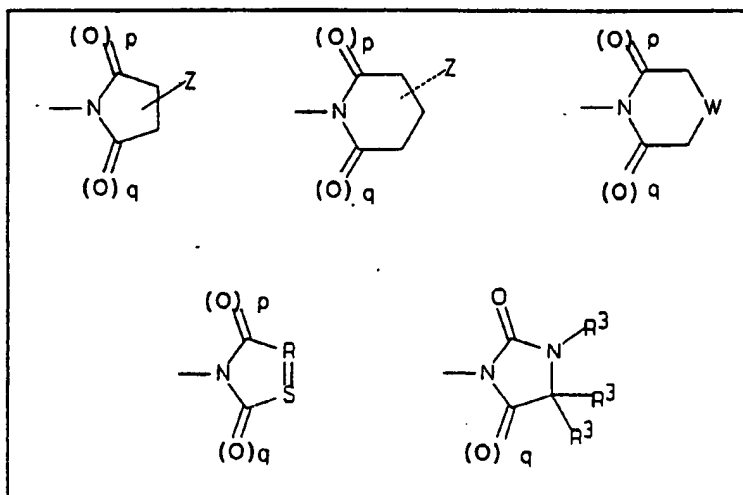
R¹⁴ may be any group defined in R⁷, SO₂R¹⁶, or COR¹⁶;

10 R¹⁵ is H, C₁₋₄ alkyl, COR⁹, CO₂R¹⁹, CON(R³)₂ where R³ maybe the same or different or SO₂R⁹;

R¹⁶ is C₁₋₄ alkyl (optionally substituted with R¹⁷);

R¹⁷ may be CO₂R³, CON(R³)₂ where R³ are the same or different, N(R³)₂ where R³ are the same or different, SO₂R⁹ or the groups:

15



20

25 R¹⁸ is CO₂R³, CON(R³)₂ where R³ are the same or different, N(R³)₂ where R³ are the same or different, NHCO₂R¹⁹, NHSO₂R⁹ or NHCOR⁹;

R¹⁹ is C₁₋₄ alkyl, C₁₋₄ alkyl-aryl or C₁₋₄ alkyl-heteroaryl;

R²⁰ is H, C₁₋₄ alkyl, C₁₋₄ alkyl-aryl or C₁₋₄ alkyl-heteroaryl;

30 R²¹ is C₁₋₆ alkyl, aryl, heteroaryl, NR³R⁷, COR⁹, SO₂N(R³)₂ where R³ are the same or different, CON(R³)₂ where R³ are the same or different, amidine or guanidine; and the salts, solvates and hydrates thereof.

2. A compound of claim 1, wherein X and Y are each C=O.

SUBSTITUTE SHEET (RULE 26)

3. A compound of claim 1 or claim 2, wherein R^1 is a C_{1-6} alkyl or C_{1-6} alkyl- AR^3 group where A is O, NR^3 or $S(O)_n$ where $n = 0-2$ and R^3 is H, C_{1-4} alkyl, heteroaryl or aryl.
4. A compound of any preceding claim, wherein R^4 is H or C_{1-4} alkyl.
- 5 5. A compound of any preceding claim, wherein R^5 is aryl (optionally substituted with R^6), heteroaryl (optionally substituted with R^6), C_{1-4} alkyl-aryl (optionally substituted with R^6), C_{1-4} alkyl-heteroaryl (optionally substituted with R^6) or C_{1-4} alkyl-heterocyclo(C_{4-6})alkyl (optionally substituted with R^6).
6. A compound of any preceding claim, wherein R^6 is H, halogen, C_{1-6} alkyl, aryl, heteroaryl, AR^3 , NR^3R^7 , COR^9 , $SO_2N(R^3)_2$ where R^3 may be the same or different, $CON(R^3)_2$ where R^3 may be the same or different, amidine or guanidine.
- 10 7. A compound of any preceding claim, wherein NR^4R^5 is a ring which is pyrrolidine (optionally substituted with R^6), piperidine (optionally substituted with R^6), morpholine or optionally-substituted piperazine as defined in claim 1.
- 15 8. A compound of any preceding claim, wherein R^7 is CO_2R^{19} or $CONHR^3$ where R^{19} is H or C_{1-4} alkyl.
9. A compound of any preceding claim, wherein R^8 is H or the group COR^9 .
10. A compound of any preceding claim, wherein R^9 is C_{1-4} alkyl or aryl.
11. A compound of any preceding claim, wherein R^{11} is H.
- 20 12. A compound of any preceding claim, wherein R^{10} is H, C_{1-6} alkyl (optionally substituted with R^{12}), C_{1-6} alkyl-aryl (optionally substituted with R^{12}) or C_{1-6} alkyl-heteroaryl (optionally substituted with R^{12}).
13. A compound of any preceding claim, wherein R^{12} is SR^8 , COR^{13} , NR^3R^7 , NR^3 , SO_2R^9 , phthalimido or succinimido.
- 25 14. A compound of any preceding claim, wherein R^{13} is OR^{20} , $N(R^3)_2$ where R^3 may be the same or different and R^{20} is H or C_{1-4} alkyl.
15. A compound of claim 1, wherein R^1 is not alkyl- COR^2 , cycloalkyl, alkyl-cycloalkyl or alkyl-heterocycloalkyl, R^1 is H, and R^{10} is C_{6-10} aryl, C_{5-10} heteroaryl, C_{1-4} alkyl- R^{12} , alkyl-aryl, C_{1-4} alkyl-heteroaryl, cycloalkyl, cycloalkenyl or alkyl-cycloalkyl, any being optionally substituted by R^{12} .
- 30 16. A compound of claim 1, selected from
2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(2-phenylethyl)amide

- 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(2-phenylmethyl)amide
 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(1H-indol-3-yl)ethyl]amide
 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(5-methoxy-1H-indol-3-yl)ethyl]amide
 5 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(6-methoxy-1H-indol-3-yl)ethyl]amide
 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(2-pyridyl)ethyl]amide
 10 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(methoxycarbonyl)ethyl]amide
 2-Sulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(phenylmethyl)amide
 2-Sulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(2-phenylethyl)amide
 2-Sulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(1H-indol-3-yl)ethyl]amide
 15 2-Sulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(5-methoxy-1H-indol-3-yl)ethyl]amide
 2-Sulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(6-methoxy-1H-indol-3-yl)ethyl]amide
 2-Sulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(2-pyridyl)ethyl]amide and
 20 2-Sulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(methoxycarbonyl)ethyl]amide.
 17. A compound of claim 1, selected from
 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(4-morpholino)amide
 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(4-methyl-3-oxopiperazino)amide
 25 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(4-acetylpiperazino)amide
 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-(2-acetylaminoethyl)amide
 30 2-Acetylsulphonyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(4-morpholino)ethyl]amide

2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[3-(1-imidazolyl)propyl]amide

2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

5 2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucine *N*-[2-(1-oxo-1-phenyl)ethyl]amide

2-Acetylsulphanyl-5-phthalimidopentanoyl-L-leucine *N*-(4-sulphonamidophenyl)amide and

10 2-Acetylsulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-(phenylmethyl)amide.

18. A compound of claim 1, selected from

2-Acetylsulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-(4-morpholino)-amide

15 2-Acetylsulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-(4-methoxyphenyl)amide

2-Acetylsulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-[(3*S*)-hexahydropyridazine]-3-carboxylic acid *N*-methanamide

2-Sulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-(2-phenylethyl)amide

20 2-Sulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-(4-morpholino)amide

2-Sulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-(4-methoxyphenyl)amide and

25 2-Sulphanyl-5-phthalimidopentanoyl-L-(*S*-methyl)cysteinyl *N*-[(3*S*)-hexahydropyridazine]-3-carboxylic acid *N*-methanamide.

19. A compound of any preceding claim, in the form of a single enantiomer or diastereomer, or a mixture of such isomers.

20. A pharmaceutical composition for use in therapy, comprising a compound of any preceding claim, and a pharmaceutically-acceptable diluent or carrier.

30 21. Use of a compound of any of claims 1 to 19, for the manufacture of a human or veterinary medicament for the treatment or prevention of a condition associated with matrix metalloproteinases or that is mediated by $\text{TNF}\alpha$.

22. Use according to claim 21, wherein the condition is selected from cancer, inflammation and inflammatory diseases, tissue degeneration, periodontal disease, ophthalmological disease, dermatological disorders, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, acute
5 infection, HIV infection, shock states, graft versus host reactions, autoimmune disease, reperfusion injury, meningitis and migraine.
23. Use according to claim 21, wherein the condition is selected from tumour growth, angiogenesis, tumour invasion and spread, metastases, malignant ascites and malignant pleural effusion.
- 10 24. Use according to claim 21, wherein the condition is selected from rheumatoid arthritis, osteoarthritis, osteoporosis, asthma, multiple sclerosis, neurodegeneration, Alzheimer's, stroke, vasculitis, Crohn's disease and ulcerative colitis.
25. Use according to claim 21, wherein the condition is selected from corneal ulceration, retinopathy and surgical wound healing.
- 15 26. Use according to claim 21, wherein the condition is selected from psoriasis, atopic dermatitis, chronic ulcers and epidermolysis bullosa.
27. Use according to claim 21, wherein the condition is selected from periodontitis and gingivitis.
28. Use according to claim 21, wherein the condition is selected from rhinitis,
20 allergic conjunctivitis, eczema and anaphylaxis.
29. Use according to claim 21, wherein the condition is selected from atherosclerosis and congestive heart failure.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 96/01135

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K5/03 C07D209/48 C07D401/12 C07D403/12 C07D413/12
 A61K38/06 A61K31/40 A61K31/435 A61K31/495 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,96 11209 (CHIROSCIENCE LTD) 18 April 1996 see claims; examples ---	1-29
P,X	WO,A,95 13289 (CHIROSCIENCE LTD ;MONTANA JOHN (GB); DICKENS JONATHON (GB); OWEN D) 18 May 1995 see claims; examples ---	1-15, 19-29
X	WO,A,95 06031 (IMMUNEX CORP) 2 March 1995 see claims; examples ---	1-15, 19-29
A	WO,A,95 09841 (BRITISH BIOTECH PHARM ;CRIMMIN MICHAEL JOHN (GB); BECKETT PAUL RAY) 13 April 1995 see claims; examples ---	1-15, 19-29
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

& document member of the same patent family

Date of the actual completion of the international search

19 September 1996

Date of mailing of the international search report

0 2. 10. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+ 31-70) 340-3016

Authorized officer

Fuhr, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/01135

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 20047 (BRITISH BIO TECHNOLOGY ;CRIMMIN MICHAEL JOHN (GB); GALLOWAY WILLIA) 14 October 1993 see claims; examples -----	1-15, 19-29

INTERNATIONAL SEARCH REPORT

international application No.

PCT/GB96/01135

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see Further Information sheet enclosed.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB96/01135

FURTHER INFORMATION CONTINUED FROM PCT/SAJ/210

OBSCURITIES

Incomplete Search

Claims searched completely: 16-18

Claims searched incompletely. 1-15, 19 - 29 Please see annex.

Annex:

In view of the extremely large number of compounds falling under claims 1-15 and 19 (completely) and the claims 20-29 as long as they refer to compounds fallingt under the scope of claims 1-15 and 19, and of the absence of any sensible support for these claims in the description, the Search Devision considers that it is not economically reasonable to draw a search report covering the entire subject matter of claims 1 -15 and 19-29. The search for claims 1-15, 19-29 has therefor been limited and includes all the real examples given in the description and covers all similar compounds having the alleged activities as well.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/01135

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9611209	18-04-96	AU-A- 3612795	02-05-96
WO-A-9513289	18-05-95	AU-A- 8113394	29-05-95
		EP-A- 0728144	28-08-96
		NO-A- 961888	09-05-96
WO-A-9506031	02-03-95	AU-A- 7569494	21-03-95
		EP-A- 0715619	12-06-96
		FI-A- 960803	22-04-96
		NO-A- 960723	23-02-96
WO-A-9509841	13-04-95	AU-A- 7787594	01-05-95
		EP-A- 0722438	24-07-96
		ZA-A- 9407799	10-07-95
WO-A-9320047	14-10-93	AU-A- 3899193	08-11-93
		EP-A- 0634998	25-01-95
		JP-T- 7505387	15-06-95
		US-A- 5525629	11-06-96
		ZA-A- 9302501	08-11-93

Serial No. 08/893,080

Filed July 15, 1997

M01846A

Hoechst Marion Roussel, Inc.

2110 E. Galbraith Road

Cincinnati, Ohio 45215